WHAT IS CLAIMED IS:

1. A method for screening a mixture of compounds against an unactivated form of a target moiety, the method comprising
    a. providing a mixture of compounds;
    b. incubating the mixture with the unactivated form of the target moiety to form compound:target complexes;
    c. separating compound:target complexes from unbound compounds and targets; and
    d. dissociating compound:target complexes;
    e. identifying the dissociated compounds which had bound to the target by passing the compound through a mass spectrometer, wherein the identified compounds bind to the target moiety with an affinity of Kd between 1 pM and 50 μM.

2. A method for screening a mixture comprising of compounds against a mixture of different forms of a target moiety, the method comprising
    a. providing a mixture of compounds;
    b. providing a mixture of ligand-bound forms and ligand-free forms of a target moiety;
    c. incubating the mixture of compounds with the mixture of the target moiety to form compound:target complexes;
    d. separating compound:target complexes from unbound compounds and target moieties;
    e. dissociating compound:target complexes; wherein the dissociated compounds separated from the target are designated new ligands;
    f. identifying new ligands from among the compounds present in compound:target complexes bound to any form of the target moiety by passing compound:target complexes through a mass spectrometer to identify ligands bound to any form of the target moiety, wherein the

identified ligands bind to the target moiety with an affinity of Kd between 1pM and 50 μM; and

g. incubating the new ligands identified in step f with ligand-bound and ligand-free forms of the target moiety, wherein steps e to f are repeated to delineate which compounds bind to the ligand-bound form versus which compounds bind to the ligand-free form of the target moiety.

3. The method of claim 1, wherein the compound mixture is mass-coded to ensure at least 90% of the compounds having a unique ion mass detectable by a mass spectrometer.

4. The method of claim 2, wherein the compound mixture is mass-coded to ensure at least 90% of the compounds having an unique ion mass detectable by a mass spectrometer.

5. The method of claim 2, wherein the mixture of target forms comprises unactivated forms, inactive forms, and active forms.

6. The method of claim 2, wherein the mixture of target forms comprises monomeric forms and multimeric forms.

7. The method of claim 2, wherein the mixture of target forms comprises ligand-bound forms and ligand-free forms.

8. The method of claim 2, wherein the mixture of target forms comprises cofactor-bound forms and cofactor-free forms.

9. The method of claim 3 or 4, wherein the mixture of target forms comprises unactivated forms and active forms.

10. The method of claim 3 or 4, wherein the mixture of target forms comprises monomeric forms and multimeric forms.

11. The method of 3 or 4, wherein the mixture of target forms comprises ligand-bound forms and ligand-free forms.

12. The method of 3 or 4, wherein the mixture of target forms comprises cofactor-bound forms and cofactor-free forms.

13. A method for discovering a test kinase inhibitor, the method comprising:

a) incubating the test kinase with a mass-coded library of compounds in the absence of ATP and/or peptide substrate;

b) separating bound compounds from unbound compounds;

c) identifying the bound compounds by mass-spectrometry; and

d) demonstrating test kinase inhibitory activity of the bound compound in a kinase inhibition assay.

14. The method of claim 13, wherein the test kinase is a full-length kinase.

15. The method of claim 13, wherein the test kinase comprises a truncated fragment of the full-length kinase that contains a catalytic domain.

16. The method of claim 13, wherein the kinase is a kinase variant or mutant.

17. The method of claim 13, wherein separating bound compounds from unbound compounds is by size exclusion chromatography.

18. The method of claim 13, wherein mass-spectrometry is done by comparing to a database of mass-coded compounds.

19. The method of claim 13, wherein the test kinase is unactivated.

20. The method of claim 13, wherein the test kinase is in a basal form exhibiting low catalytic activity.

21. The method of claim 13, wherein the test kinase is activated.

22. The method of claim 14, wherein the test kinase is partially active relative to its physiologically active state.

23. A method of designing an inhibitor, the method comprising

a) comparing an unactivated test kinase to an unactivated reference kinase whose 3-dimensional structure is known;

b) identifying an allosteric binding site; and

c) designing an inhibitor based on the allosteric binding site.

24. The method of claim 23, wherein step c) comprises the steps

c1) designing a scaffold based on topological and electronic properties of the allosteric binding site; and

c2) designing a mass-coded library based on the scaffold.

25. The method of claim 23, wherein step c) comprises providing a mass-coded library.

26. The method of claim 24, further comprising step d) screening the mass-coded library for compounds that bind to the test kinase; and e) determining whether the kinase binder inhibits the test kinase, thereby designing an inhibitor of the test kinase.

27. The method of claim 25, wherein screening comprises affinity screening with the test kinase.

28. The method of claim 23, wherein the reference kinase is selected from the group consisting of kinases with Protein Data Bank identifiers 1kv1 chain a and 1kv2 chain a.

29. The method of claim 23, wherein the reference is selected from the group consisting of kinases with Protein Data Bank identifiers 1iep chain a, 1iep chain b, 1fpu chain a, and 1fpu chain b.

30. The method of claim 23, wherein the reference kinase has a Protein Data Bank identifier 1irk.

31. The method of claim 23, wherein the reference is selected from the group consisting of kinases with Protein Data Bank identifiers 1g3n chain a and 1g3n chain b.

32. The method of claim 23, wherein the allosteric binding site is spatially distinct from the ATP binding site and the activation loop.

33. The method of claim 23, wherein the allosteric binding site is identified by locating a DFG motif.

34. The method of claim 33, wherein the DFG motif comprises a DWG or a DLG sequence.

35. The method of claim 33, wherein the DFG motif is greater than 11 Å and less than 20 Å in distance from an helix alpha-C, and the DFG motif is in the DFG-out conformation.

36. The method of claim 35, wherein the helix alpha-C is homologous in relative 3-dimensional location to insulin receptor kinase helix alpha C containing Val1050-Met1051.

37. The method of claim 35, wherein the helix alpha-C is homologous in relative 3-dimensional location to c-abl helix alpha-C containing Val289-Met290.

38. The method of claim 23, further comprising determining whether the potential binder inhibits the test kinase.

39. A method of designing an inhibitor of a test kinase, the method comprising

a) comparing the test kinase to a reference kinase whose 3 dimensional structure is known;

b) identifying an allosteric binding site;

c) designing a scaffold targeting the allosteric binding site;

d) providing a mixture of compounds based on the scaffold;

e) identifying ligands for the allosteric site by affinity screening against the kinase; and

f) demonstrating kinase inhibitory activity by the ligand in a kinase assay.

40. The method of claim 39, wherein the test kinase and the reference kinase are unactivated.

41. The method of claim 39, wherein the test kinase is a full-length kinase.

42. The method of claim 39, wherein the test kinase comprises a truncated fragment of the full-length kinase that contains a catalytic domain.

43. The method of claim 39, wherein the test kinase is in a basal form exhibiting low catalytic activity.

44. The method of claim 39, wherein the test kinase is activated.

45. The method of claim 39, wherein the test kinase is partially active relative to its physiologically active state.

46. The method of claim 39, wherein step c) comprises designing a scaffold based on topological and electronic properties of the allosteric binding site.

47. The method of claim 39, wherein the mixture of compounds based on the scaffold consists of a mass-coded library of potential kinase ligands.

48. The method of claim 39, wherein step e) comprises the steps of

e1) incubating the test kinase with the mass-coded library to allow ligands of the library to bind the test kinase;

e2) separating kinase-bound ligands from unbound ligands;

e3) separating the kinase from the bound ligand; and

e4) identifying bound compounds by mass-spectrometry;

49. A method of designing an inhibitor, the method comprising

a) comparing a test kinase to a reference kinase whose 3-dimensional structure is known;

b) identifying an allosteric binding site;

c) designing a scaffold targeting the allosteric binding site; and

d) providing mixtures of compounds based on the scaffold.

50. The method of claim 49, the method further comprising

e) identifying ligands for the allosteric site by affinity screens against the kinase.

51. The method of claim 50, the method further comprising

f) demonstrating kinase inhibitory activity.

52. A method of designing an inhibitor of a test kinase, the method comprising

a) using a 3-dimensional structure of a reference kinase to locate a DFG motif in the test kinase;

b) identifying an allosteric binding site formed in the test kinase by the DFG motif in the DFG-out conformation, wherein the allosteric binding site is spatially distinguishable from an ATP binding site and an activation loop;

c) designing a scaffold based on the allosteric binding site;

d) providing a mixture of compounds based on the scaffold;

e) screening the mixture of compounds for kinase binders;

f) separating kinase binders from non-binders;

g) identifying the kinase binders by mass-spectrometry;

h) optionally contacting the binder to the kinase under conditions and for a time sufficient to allow the binder to bind to the kinase; and

e) demonstrating that the kinase is rendered non-functional or less functional by the binder; thereby identifying an inhibitor of a test kinase.

53. A method of designing an inhibitor of a test kinase, the method comprising

a) using a 3-dimensional structure of a reference kinase to locate a DFG motif in the test kinase;

b) identifying an allosteric binding site formed by the DFG motif in the DFG-out conformation, wherein the allosteric binding site is spatially distinct from an ATP binding site and an activation loop;

c) designing a scaffold based on the allosteric binding site;

d) synthesizing a mixture of compounds based on the scaffold;

e) identifying ligands for the allosteric site by affinity screens of the mixtures of compounds against the kinase; and

f) demonstrating kinase inhibitory activity.

54. The method of claim 41, 42, 49, 52, or 53, wherein the test kinase is unactivated.

55. The method of claim 39, 49, 52, or 53, wherein the reference kinase is selected from the group consisting of kinases with Protein Data Bank identifiers 1kv1 chain a and 1kv2 chain a.

56. The method of claim 39, 49, 52, or 53, wherein the reference kinase is selected from the group consisting of kinases with Protein Data Bank identifiers 1iep chain a, 1iep chain b, 1fpu chain a, and 1fpu chain b.

57. The method of claim 39, 49, 52, or 53, wherein the reference kinase has a Protein Data Bank identifier 1irk.

58. The method of claim 39, 49, 52, or 53, wherein the reference kinase is selected from the group consisting of kinases with Protein Data Bank identifiers 1g3n chain a and 1g3n chain b.

59. The method of claim 39, 49 or 52, wherein the allosteric binding site is spatially distinct from the ATP binding site and the activation loop.

60. The method of claim 13, 23, 39, 49, 52, or 53, wherein the test kinase is p38 MAP kinase.

61. The method of claim 13, 23, 39, 49, 52, or 53, wherein the test kinase is c-abl.

62. A method of identifying an inhibitor of a test kinase, the method comprising

a) providing a test compound that binds to the test kinase without physically binding to an ATP binding site on the test kinase, wherein the test compound binds to an allosteric site present when a DFG motif of the test kinase is in a DFG-out position;

b) determining if ATP can bind to the ATP binding site on the test kinase, wherein indirectly interfering with the binding of ATP to the test kinase by binding of the test compound to the allosteric site of the test kinase identifies the test compound as a kinase inhibitor; and

c) optionally performing a kinase assay in the presence or absence of the inhibitor bound to the test kinase, wherein decreased kinase activity in the presence of the test compound relative to kinase activity in the absence of the test compound further confirms the test compound is an inhibitor of the test kinase.

63. A method of identifying an inhibitor of a test kinase, the method comprising

a) providing a test compound that binds to the test kinase without physically binding to an ATP binding site on the test kinase; and

b) determining if ATP can bind to the ATP binding site on the test kinase, wherein interfering with the binding of ATP to the test kinase by binding of the test compound to the test kinase identifies an inhibitor of the test kinase, wherein the test compound confines a DFG motif of the test kinase in a DFG-out position.

64. A method of identifying an allosteric binding site spatially distinguishable from an ATP binding site and an activation loop, the method comprising

a) comparing a test kinase to a reference kinase whose 3-dimensional structure is known;

b) locating a DFG motif in the test kinase based on its location in the reference kinase; and

c) measuring shortest distance between an alpha carbon residue in alpha helix C and a non-backbone heavy atom of phenylalanine, leucine or tryptophan of the DFG motif of the test kinase, wherein a distance of greater than 11 Å and less than 20 Å characterizes the DFG motif of the test kinase as in the DFG-out conformation; and

d) identifying amino acids, partially forming a concave pocket formed by the DFG motif in the DFG-out conformation, by locating amino acids in the test kinase analogous to amino acids X through Y of the reference kinase, wherein locating the concave pocket identifies the allosteric binding site.

65. A method of identifying an allosteric binding site, spatially distinct from an ATP binding site and an activation loop, for an inhibitor of a test kinase, the method comprising

a) locating a DFG motif in the test kinase by comparing tertiary structure of the test kinase to tertiary structure of a kinase whose 3-dimensional structure is known;

b) allowing a test compound to bind to the allosteric site when the DFG motif is in an DFG-out position;

c) determining if the test compound inhibits the activity of the test kinase; and

d) determining if the test compound binds the test kinase at an allosteric site formed when the DFG motif is in a DFG-out conformation, wherein binding of the test compound such that the DFG motif is confined in the DFG-out position, identifies the allosteric binding site of the test kinase.

66. The method of any one of claim 33, 52, 53, 64, or 65, wherein locating the DFG motif comprises multiple sequence alignment.

67. The method of claim 65, wherein determining if the test compound inhibits the activity of the test kinase comprises a kinase assay.

68. The method of claim 65, wherein determining if the test compound binds the test kinase at an allosteric site formed when the DFG motif is in the DFG-out conformation comprises labeling the test compound.

69. The method of claim 65, wherein determining if the test compound binds the test kinase at an allosteric site formed when the DFG motif is in the DFG-out conformation comprises producing and analyzing an x-ray crystal of the test compound bound to the kinase.

70. An inhibitor of the method of claim 13, 23, 39, 49, 52, 53, 62, or 63.

71. The inhibitor of claim 70, wherein the inhibitor is not an inhibitor of p38MAPK, c-abl, or insulin receptor kinase.

72. The inhibitor of claim 70, wherein the inhibitor inhibits p38MAPK.

73. The inhibitor of claim 70, wherein the inhibitor inhibits c-abl.

74. The inhibitor of claim 70, wherein the inhibitor inhibits insulin receptor kinase.

75. A pharmaceutical composition comprising the inhibitor of claim 63 or 64.

76. A kit comprising any one of the inhibitors of claim 70.

77. A method of inhibiting kinase activity in a subject comprising the step of administering to the subject a compound comprising the inhibitor of claim 70.

78. The method of claim 77, wherein the subject is a mammal.

79. The method of claim 78, wherein the mammal is a human.

80. A method of treating a kinase-mediated disease or disease symptoms in a subject comprising administration to said subject of a compound comprising the inhibitor of claim 70.

81. The method of claim 80, wherein the subject is a mammal.

82. The method of claim 81, wherein the mammal is a human.

83. A method of treating disease or disease symptoms in a subject comprising the step of administering to said subject of a compound comprising the inhibitor of claim 70.

84. The method of claim 83, wherein the subject is a mammal.

85. The method of claim 84, wherein the mammal is a human.

86. A method of making a pharmaceutically useful composition comprising combining the inhibitor of claim 70 with one or more pharmaceutically acceptable carriers.

87. The inhibitor of claim 70, further comprising combining an additional therapeutic agent.

88. The method of claim13, 23, 39, 42, 44, 49, 52, or 53, wherein the DFG in the DFG-out position induces formation of a concave pocket, wherein the surface of the concave pocket is formed in part by amino acids X through Y, wherein X is a first amino acid in a contiguous sequence of amino acids and Y is a last amino acid in the contiguous sequence of amino acids that form in part the concave pocket.

89. The method of claim 88, wherein amino acids X through Y consist of Leu 104 through Ala 111 of a protein whose PDB accession code is 1kv2.

90. The method of claim 88, wherein amino acids X through Y consist of amino acids homologous to Leu104 through Ala111, of a protein whose PDB accession code is 1kv2, as determined by sequence alignment analysis.